compensated by another, functionally overlapping DDR pathway whose activity may be increased, causing resistance to DNA-damaging radiotherapy and chemotherapy. Therefore, the DDR response makes an ideal target for therapeutic intervention by preventing or reversing therapy resistance or by using a synthetic lethality approach to specifically kill cancer cells that are dependent on a compensatory DNA repair pathway for survival in the context of cancer-associated oxidative and replicative stress. However, in the context of DNA replication several DNA repair pathways are gathered with overlapping functions, as demonstrated by the synthetic lethal interaction between the DNA double strand repair pathway homologous recombination (HR) and the base excision repair pathway (BER) as well as between checkpoint signaling (ATR/CHK1) and the Fanconi anaemia pathway. As the number of inhibitors that target components of these pathways expands the potential for using these synthetic lethal interactions increases, provided that the exploitable defects in the tumour can be identified with suitable biomarkers. These hypotheses are currently being tested in the laboratory and translated into clinical studies.

Teaching Lecture: Anal cancer: current guidelines and remaining questions

SP-0182
Anal cancer: current guidelines and remaining questions

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Introduction - Anal cancer is a rare disease but its incidence is rising rapidly. The majority of tumours are squamous cell carcinoma or its histological variants. Despite its rarity phase III clinical trials have been successfully performed. The "first generation" of phase III trials tested the benefit of concurrent chemotherapy when added to radiotherapy. This led to Mitomycin C 5Fluorouracil and radiotherapy (CRT) becoming the standard of care. The shift from radical surgery with permanent stoma to non-surgical combined modality treatment was achieved through these clinical trials and recent published evidence confirms the impact on population based practice. The "second generation" of phase III did not change the standard of care. They demonstrated no benefit from the addition of neoadjuvant or maintenance chemotherapy to CRT and no improvement in outcome from the use of cisplatin based CRT. The ESMO-ESSO-ESTRO and NCCCN guidelines provide evidence based recommendations for the management of anal cancer and aspects of the guidelines will be reviewed during this teach lecture.

Staging – Whilst it is important to identify the relatively small minority of patients who present with synchronous metastatic disease, the main role of imaging is to determine the extent of disease in the pelvis prior to CRT. Although pelvic MR is not mandated in the guidelines it provides superior anatomical images of the primary tumour which is very helpful for conventional CT planning and delineation of the gross tumour volume. CT-PET is also not mandated but is shown to upstage a minority of patients from a "N0" category to "N+." Examples of this will be presented and discussed. Radiotherapy dose fractionation – there is wide variation in the prescribed radiotherapy dose to both gross tumour volume and clinical target volumes. Many centres will use higher doses of 60Gy or greater to more advanced tumours. However, to date randomized clinical trials have not demonstrated any clear benefit for dose escalation. There is also a paucity of late toxicity and patient reported outcome data to determine the impact of such an approach.

Radiotherapy technique and target volume definition - The use of IMRT has significantly increased in the treatment of anal cancer and its use is supported by the RTOG 0529 phase II trial. Although IMRT may be preferred and will reduce acute genital toxicity, careful target volume definition and delineation of organs at risk and high quality QA are required to ensure accurate treatment delivery. The AGITG contouring atlas has been very helpful to clinicians. The UK approach to introducing IMRT will be discussed.

Response assessment - Clinical and radiological assessment is required to both identify early local treatment failures and to establish whether complete response had been achieved. The European guidelines recommend assessment at 11, 18 and 26 weeks from the start of CRT. Recent published data will be reviewed. The optimal timing and imaging is the subject for further research.

Follow up - Most centres will review patients at least three monthly in the first two years, with approximately 80% of pelvic recurrences occurring during this period. The duration of follow up and the intensity of imaging varies widely.

Late toxicity - Although it is assumed that most patients will experience improved quality of life with CRT rather than radical surgery there is limited data on the impact of late radiotherapy effects on patients. New data is required particularly with the use of IMRT to understand this in more detail. An anal cancer specific module quality of life module is in development through the EORTC.

Treatment of metastatic disease - Approximately 10-20% of patients will develop metastatic disease. There is no consensus on the best first or second line chemotherapy regimens and reports of the outcomes following surgical or non surgical treatment of oligometastatic disease are sparse. The InterAAcT trial is an international randomized phase II study comparing cisplatin 5FU with Carboplatin and Paclitaxel and will be discussed

Future research - Future clinical trials will provide more information on outcome and late toxicity with the use of IMRT. The UK led PLATO trial consortium are conducting a "platform" type trial with the ACT3 ACT4 and ACT5 trials addressing specific research questions. ACT3 evaluates a selective use of reduced dose CRT for patients with T1N0 anal margin tumours; ACT 4 will compare standard versus lower dose CRT for early stage disease; ACT5 will test two IMRT SIB dose escalation CRT schedules against standard dose CRT.

Teaching Lecture: Radiotherapy and immune-therapy, biological basis and potential for future clinical trials

SP-0183
Radiotherapy and immune-therapy, biological basis and potential for future clinical trials

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The immunosuppressive effects of radiation therapy have long been the only one considered. Dying cancer cell may release signals which activate the surrounding immune cells, namely through the immunological cell death process. Irradiation can also increase the diversity of tumor neo antigens which are crucial to the induction of adaptive antitumor immunity. It has recently been shown that the inhibition of immune inhibitory checkpoints synergizes with ionizing radiation in preclinical models. Hypoxia is one of the key factors influencing clinical outcome after radiotherapy responsible for reduced local control that will influence overall survival, as may the hypoxic conditions by increasing malignant progression. For decades, hypoxia was thought to act primarily on tumor cells resistance, namely the number of clonogenic cancer stem cells surviving after radiation treatment. Increased cellular turnover and hypoxia promote the production and release of large amounts of immunosupressive adenosine into the local microenvironment. Hypoxia can induce HIF-1a-dependent expression of arginase-1 and M2 polarization of macrophages. Recent data suggest that the immune contexture of tumors might be correlated with outcome after irradiation. The purpose of tumor immunotherapy is based on the principle that reversal of tolerance to immunogenic tumors would be able to activate an immune response against tumor cells. The importance of the immune component into the process of tumor response to radiation offers novel opportunities for therapeutic interventions.